REMARKS

Any fee that may be due in connection with the filing of this paper may be charged to Deposit Account No. 50-1213. If a Petition for Extension of Time is needed, this paper is to be considered such Petition.

Claims 1-64, 69-83, 87-89, 93 and 99-121 are pending herein. No amendments to the claims are made herein.

REJECTION OF CLAIMS 1-64, 69-83, 87-89, 99-112 AND 117-119 UNDER 35 U.S.C. §103(a)

Claims 1-64, 69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2)*:303-322) and the Physician's Desk Reference (PDR) entry for fluticasone propionate. Applicant respsectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

[I]n order to establish a prima facie case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The instant claims

Instant claim 1 is directed to a pharmaceutical composition, containing (i) formoterol, or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof; in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Claims 2-64, 69-76, 81-83, 87-89, 99-108, 111 and 112 are all dependent on claim 1 and therefore incorporate all of the limitations of claim 1.

Claim 77 is directed to a nebulized suspension or solution, containing (i) formoterol or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof; in a pharmacologically suitable fluid.

Claim 78 is directed to a kit, containing (a) an aqueous composition containing (i) formoterol or a derivative thereof, and (ii) a steroidal anti-inflammatory agent or a derivative thereof, formulated for single dosage administration; and (b) a nebulizer. Claims 79-80, 109 and 110 are dependent on claim 78 and therefore incorporate all of the limitations of claim 78.

Claim 117 is directed to a combination, containing a composition containing formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration for direct administration to a subject in need thereof; and a composition containing a bronchodilating steroid, or a derivative thereof.

Differences between the cited references and the instant claims

Hochrainer *et al.*

Applicant has previously argued, *inter alia*, that Hochrainer *et al.* teaches two compositions: 1) an "active substance concentrate;" and 2) a "pharmaceutical preparation."

"Active substance concentrate"

The "active substance concentrate" is not formulated at a concentration for direct administration to a subject in need thereof. The "active substance

concentrate" is taught as a "highly concentrated" solution or suspension (*i.e.*, greater than 10 mg/mL, preferably 75 to 500 mg/mL) that is stable for a period of several months, possibly up to several years without any deterioration in the pharmaceutical quality (see, *e.g.*, column 1, lines 55-61; column 2, lines 4-7; and claim 1 of Hochrainer *et al.*). The "highly concentrated" "active substance concentrate" of the reference is not suitable for direct administration to a subject in need thereof. See, *e.g.*, column 2, lines 1-4:

> The term "highly concentrated" means a concentration of the active substance which is usually too high to enable the corresponding solution or suspension to be used therapeutically for inhalation without being diluted.

See also, *e.g.*, column 1, lines 47-52:

> The active substance concentrate according to the invention may be converted, by diluting with a pharmacologically acceptable liquid which optionally contains pharmaceutical adjuvants and additives, into a pharmaceutical preparation (aerosol formulation) which is converted by means of a nebulizer into an inhalable aerosol.

See also, *e.g.*, column 4, lines 9-13:

> The active substance concentrate according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation. As already explained, use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation).

Thus the "active substance concentrate" of Hochrainer *et al.* is merely a means for the storage of highly concentrated solutions of formoterol, and is not formulated at a concentration for direct administration to a subject in need thereof.

"Pharmaceutical preparation"

Furthermore, Applicant has previously argued that Hochrainer *et al.* teaches that formoterol compositions formulated at a concentration for direct administration to a subject in need thereof (*i.e.*, "pharmaceutical preparations") are not stable, and therefore the reference teaches away from the claimed subject matter. Applicant pointed to column 1, lines 30-35, where the reference teaches:

> In the past it has been found that liquid aerosol formulations of formoterol are not suitable for use in inhalers intended for ambulatory inhalation treatment since *formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time.* (emphasis added)

In response to Applicant's arguments, the Final Office Action state "[n]ote that nowhere does Hochrainer teach that its composition suitable for direct administration is unstable." The Final Office Action also states "[n]ote that [the] quotation [above] merely reports what was known in the art prior to the Hochrainer patent and cannot be construed to mean that the Hochrainer pharmaceutical composition itself will be unstable." Applicant respectfully disagrees with the Final Office Action's characterization of the teachings of Hochrainer *et al.*

The above-referenced quotation from Hochrainer *et al.* states more that the prior art knowledge. It states unequivocally that formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time. This is not stated merely in the context of prior compositions, but rather is stated as an alleged property of formoterol itself. Therefore, Hochrainer *et al.* teaches away from the subject matter of the instant claims.

Example 3 of Hochrainer *et al.*

A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed subject matter. See, *e.g., W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). A *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. See, *e.g., In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

The reference teaches in Example 3 that a suspension is stable for 6 months at 40 °C. This suspension is comparable to the active substance concentrates of Examples 1 and 2 of the reference.

More importantly, Hochrainer *et al.* states in Example 3 (column 6, lines 55-59) that an aqueous solution of formoterol at pH 5.0 is not stable during long term storage (only 10% remaining after 3 months at 40 °C). This solution corresponds to the pharmaceutical preparations of Examples 1 and 2 of Hochrainer *et al.* Thus, Hochrainer *et al.* does teach in Example 3 that its "pharmaceutical preparation" is

unstable during long term storage. Therefore, Hochrainer *et al.* teaches away from the instant claims and the instant claims are not obvious over the teachings of Hochrainer *et al.*

Bartow *et al.* and the PDR do not cure the defects of Hochrainer *et al.*

Bartow *et al.* and the PDR entry for FLOVENT® do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Neither Bartow *et al.* nor the PDR teach or suggest modification of the "active substance concentrate" or the "pharmaceutical preparation" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of the instant claims. Bartow *et al.* and the PDR do not teach or suggest modifying the "active substance concentrate" or the "pharmaceutical preparation" of Hochrainer *et al.* such that the composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof, as required by the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claims 1-64, 69-83, 87-89, 99-112 and 117-119 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

REJECTION OF CLAIM 93 UNDER 35 U.S.C. §103(a)

Claim 93 is rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2)*:303-322) and the Physician's Desk Reference (PDR) entry for fluticasone propionate, and further in view of the PDR entries of albuterol, accolate and Zyflo. Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Claim 93

Instant claim 93 is directed to the pharmaceutical composition of claim 1, as described above, further containing one or more of (a) to (j) as follows: (a) a ß2-adrenoreceptor agonist; (b) a dopamine (D2) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lypoxygenase inhibitor; or (j) an anti-IgE antibody.

Differences between the cited references and claim 93

Hochrainer *et al.*

The teachings of Hochrainer *et al.* are discussed in detail above. As noted above, Hochrainer *et al.* states in Example 3 (column 6, lines 55-59) that an aqueous solution of formoterol at pH 5.0 is not stable during long term storage (only 10% remaining after 3 months at 40 °C). This solution corresponds to the pharmaceutical preparations of Examples 1 and 2 of Hochrainer *et al.* Thus, Hochrainer *et al.* does teach in Example 3 that its "pharmaceutical preparation" is unstable during long term storage. Therefore, Hochrainer *et al.* teaches away from instant claim 93 and the instant claim 93 is not obvious over the teachings of Hochrainer *et al.*

Bartow *et al.* and the PDR do not cure the defects of Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT® and the PDR entries for albuterol, accolate and Zyflo do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. The PDR entries for albuterol, accolate and Zyflo teach that albuterol, accolate and Zyflo are all known to be effective in treating asthma.

Instant claim 93 is directed to a pharmaceutical composition of claim 1, further containing one or more of (a)-(j). Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow et al. nor the PDR entries cited above teach or suggest modification of the "active substance concentrate" or the "pharmaceutical composition" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of instant claim 93. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claim 93 is not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

REJECTION OF CLAIMS 113-116, INSOFAR AS THE READ ON IPRATROPIUM BROMIDE, UNDER 35 U.S.C. §103(a)

Claims 113-116, insofar as the read on ipratropium bromide, are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.*, Bartow *et al.* and the PDR, as above, and further in view of Hardman *et al.* (*Goodman Gilman's The Pharmacological Basis of Therapeutics*, 1996, page 665). Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Instant claims 113-116

Instant claim 113 is directed to the pharmaceutical composition of claim 1, as described above, further comprising an anticholinergic agent. Claims 114-116 are dependent on claim 113 and therefore incorporate all of the limitations of this claim.

Differences between the cited references and the instant claims

Hochrainer *et al.*

The teachings of Hochrainer *et al.* are discussed in detail above. As noted above, Hochrainer *et al.* states in Example 3 (column 6, lines 55-59) that an aqueous solution of formoterol at pH 5.0 is not stable during long term storage (only 10% remaining after 3 months at 40 °C). This solution corresponds to the pharmaceutical preparations of Examples 1 and 2 of Hochrainer *et al.* Thus, Hochrainer *et al.* does teach in Example 3 that its "pharmaceutical preparation" is unstable during long term storage. Therefore, Hochrainer *et al.* teaches away from instant claims 113-116 and nstant claims 113-116 are not obvious over the teachings of Hochrainer *et al.*

Bartow *et al.*, the PDR and Hardman *et al.* do not cure the defects of Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT® and Hardman *et al.* do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Hardman *et al.* teaches that ipratropium bromide is an anticholinergic agent useful in treating asthma.

Instant claims 113-115 (in so far as they read on ipratropium bromide) and 116 are directed to a pharmaceutical composition of claim 1, further containing an anticholinergic agent. Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow *et al.*, the PDR nor Hardman *et al.* teach or suggest modification of the "active substance concentrate" or the "pharmaceutical preparation" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claims 113-115 (in so far as they read on ipratropium bromide) and 116 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Hardman *et al.*

REJECTION OF CLAIMS 113-116, INSOFAR AS THE READ ON TIOTROPIUM BROMIDE, AND 120-121 UNDER 35 U.S.C. §103(a)

Claims 113-116, insofar as the read on tiotropium bromide, and 120-121 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.*, Bartow *et al.* and the PDR, as above, and further in view of Leckie *et al.* (*Novel Therapy of COPD*, abstract, January 2000). Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Instant claims 113-116 and 120-121

Instant claim 113 is directed to the pharmaceutical composition of claim 1, as described above, further comprising an anticholinergic agent. Claims 114-116, 120 and 121 are dependent on claim 113 and therefore incorporate all of the limitations of this claim.

Differences between the cited references and the instant claims

Hochrainer *et al.*

The teachings of Hochrainer *et al.* are discussed in detail above. As noted above, Hochrainer *et al.* states in Example 3 (column 6, lines 55-59) that an aqueous solution of formoterol at pH 5.0 is not stable during long term storage (only 10% remaining after 3 months at 40 °C). This solution corresponds to the pharmaceutical preparations of Examples 1 and 2 of Hochrainer *et al.* Thus, Hochrainer *et al.* does teach in Example 3 that its "pharmaceutical preparation" is unstable during long term storage. Therefore, Hochrainer *et al.* teaches away from instant claims 113-116 and 120-121, and the instant claims 113-116 and 120-121 are not obvious over the teachings of Hochrainer *et al.*

Bartow *et al.*, the PDR and Leckie *et al.* do not cure the defects of Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT® and Leckie *et al.* do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Leckie *et al.* teaches that tiotropium bromide is a known bronchiodilator employed in treating asthma.

Instant claims 113-115 (in so far as they read on tiotropium bromide) and 120-121 are directed to a pharmaceutical composition of claim 1, further containing an anticholinergic agent. Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow *et al.*, the PDR or Leckie *et al.* teach or suggest modification of the "active substance concentrate" or the "pharmaceutical preparation" taught in

Hochrainer *et al.* to arrive at the pharmaceutical compositions used in the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claims 113-115 (in so far as they read on tiotropium bromide) and 120-121 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Leckie *et al.*

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In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully Submitted,
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